Remarks

Claim 1-6 are currently pending in the application. In order to advance prosecution, Applicants have amended claim 1 and canceled claim 3. The cancellation of claim 3 makes no admission regarding the patentability of this subject matter and should not be so construed. A complete listing of all the claims, in compliance with the revised amendment format, is shown above. The amendments to the pending claims were made to clarify the scope of coverage and more particularly point out and distinctly claim the present invention. These amendments are made without prejudice, do not constitute amendments to overcome any prior art rejections, and do not present any new matter.

Applicant gratefully acknowledges the withdrawal of all rejections and objections as set forth in the previous Office Action.

The Office Action cites to the abstracts of several references rather than the underlying full-text documents. Applicant wishes to make the full-text documents of record in the application. These references are also listed on the attached PTO Form 1449. Copies of the references are also attached. This Information Disclosure Statement is in compliance with the continuing duty of candor as set forth in 37 C.F.R. § 1.56. It is requested that each document cited be given thorough consideration and that it be cited of record in the prosecution history of the present application by initialing on Form PTO-1449. Such initialing is requested even if the Examiner does not consider a cited document to be sufficiently pertinent to use in a rejection, or otherwise does not consider it to be prior art for any reason, or even if the Examiner does not believe that the guidelines for citation have been fully complied with. This is requested so that each document becomes listed on the face of the patent issuing on the present application.

Portions of the references may be material to the examination of the pending claims, however no such admission is intended. 37 C.F.R. 1.97 (h). The references have not been reviewed in sufficient detail to make any other representation and, in particular, no representation is intended as to the relative importance of any portion of the references. This Statement is not a representation that the cited references have effective dates early enough to be "prior art" within the meaning of 35 U.S.C. sections 102 or 103.

Election of Species Requirement

Applicant gratefully acknowledges the reconsideration of the species requirement, such that the claims have presently been examined to the extent that they read on the species of "terminal differentiation" and "apoptosis."

Discussion of the 35 U.S.C. § 103(a) Rejection(s)

Claims 1, 2, 5, and 6 are rejected under 35 U.S.C. § 103(a) as being obvious over Bacus (U.S. 5,288,477) ("Bacus") in view of the abstract of Smith and al-Mounhri (Biomed. Pharmacother., 1998, Vol. 52, pp. 116-121) ("Smith") and any of Porter (U.S. 5,498,522) ("Porter") or Los *et al.* (U.S. 6,447,997) ("Los") or Barbera-Guillem *et al.* (U.S. 5,536,642) ("Barbera-Guillem"). Applicant respectfully traverses this rejection.

An analysis for obviousness requires a determination of the scope and content of the prior art, that the differences between the prior art and the claims at issue be ascertained, and that the level of ordinary skill in the pertinent art be understood. *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966). To establish a *prima facie* case of obviousness, the Office must show three basic criteria: (1) there must be a suggestion or motivation to combine the reference teachings; (2)

there must be a reasonable expectation of success; and (3) all of the claimed limitations must be taught or suggested in the combined prior art references. M.P.E.P. § 2143.

In view of the continuing obviousness rejections, Applicant emphasizes the clear mandate of the patent statutes and the relevant and extensive case law concerning obviousness, as well as the internal guidelines of the Patent Office itself, that "[t]he following tenets of patent law must be adhered to:

(A) The claimed invention must be considered as a whole;

(B) The references must be considered as a whole and must suggest the desirability and thus the obviousness of making the combination;

(C) The references must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention; and

(D) Reasonable expectation of success is the standard with which obviousness is determined."

M.P.E.P. § 2141 (citing *Hodosh v. Block Drug Co.*, 229 U.S.P.Q. 182, 187 n.5 (Fed. Cir. 1986)). Applicant respectfully contends that, at the least, the Office Action has impermissibly failed to consider the claimed invention as a whole, and has failed to establish that even *if* the references *could* have been combined (*i.e.*, that there was teaching, suggestion or motivation in the cited references themselves *to* combine) there would not have been a reasonable expectation of success of arriving at the claimed invention before Applicant's disclosure. At its best, the Office Action may support an argument that the claimed invention was obvious to try, which has been expressly rejected as the standard for obviousness under 35 U.S.C. § 103. M.P.E.P. § 2145(X)(B).

At the outset, Applicant notes that the Office Action cites to the abstract of Smith, rather than the underlying full text document, to support this obviousness rejection. According to the internal guidelines of the Patent Office, however, "[c]itation of and reliance upon an abstract without citation of and reliance upon the underlying scientific document is generally inappropriate where both the abstract and the underlying document are prior art." M.P.E.P. 706.02(II). The M.P.E.P. also requires that the record "be clear as to whether the examiner is relying upon the abstract or the full text document to support a rejection." *Id.* This is necessary because it is possible "that the full text document will include teachings away from the invention that will preclude an obviousness rejection under 35 U.S.C. 103, when the abstract alone appears to support the rejection." *Id.* The M.P.E.P. concludes that it is only appropriate under limited circumstances to make a rejection in a non-final Office Action based in whole or in part on the abstract only without relying on the full text document. *Id.* Nevertheless, "[w]hen an abstract is used to support a rejection, the evidence relied upon is the facts contained in the abstract, not additional facts that may be contained in the underlying full text document." *Id.* Applicant submits the underlying full text document of Smith with this Response and respectfully requests it be given thorough consideration and that it be cited of record in the prosecution history of the present application.

The present invention is directed to methods for determining a response to administration of a chemotherapeutic or chemopreventive agent to an individual, wherein said method comprises collecting a tissue or cell sample from an individual both before and after exposing the individual to a chemotherapeutic or chemopreventive agent, immunohistochemically staining both samples using a detectably labeled antibody directed against a biological marker, wherein said biological marker is p21, p27, p16, TGF-ß, or SA-ß-Gal, measuring the optical density of

the stained samples, and determining whether expression of the biological marker was increased following exposure to the chemotherapeutic or chemopreventive agent. As such, the present invention is concerned with measuring expression of the biological markers in tissue or cell samples from an individual both before and after treatment with a chemotherapeutic or chemopreventive agent and using those results to determine if the individual actually responded to treatment.

None of the cited references, alone or in combination, teach or suggest the instantly claimed method. As the Applicant has previously emphasized, Bacus teaches a method for *prognosticating* the effectiveness of a therapeutic agent in the treatment of a cancer by measuring the ability of the therapeutic agent to induce terminal differentiation wherein malignant cells of the cancer overexpress an oncogene product, the method comprising obtaining from a human having cancer *a single* biopsy comprising viable malignant cells which overexpress at least one oncogene product; dividing said biopsy into a first and second portion; treating the first portion with a compound having specific binding affinity for said oncogene product; maintaining said first and second portions in physiologically acceptable medium for an amount of time sufficient to induce maturation in the viable malignant cells of the first portion; and comparing the percentage of cells in the first portion which exhibit markers of terminal differentiation with the percentage of cells in the second portion which exhibit markers of terminal differentiation, wherein the effectiveness of treatment is correlated with the degree of terminal cell differentiation. Accordingly, because Bacus only teaches obtaining a *single* biopsy from a human having a cancer, it certainly does not teach or suggest the presently claimed methods that require collecting *both* a first and second tissue or cell sample from an individual, *both* before and after exposing the individual to a chemotherapeutic or chemopreventive agent. Further,

Bacus teaches how to *prognosticate* or *predict* a response to chemotherapy, whereas the present invention is drawn to methods of determining the *actual* response to chemotherapy. Moreover, Bacus does not teach, much less suggest, the use of p21, p27, p16, TGF-ß, or SA-ß-Gal ad biological markers. Thus, Bacus does not teach or suggest the presently claimed invention.

The Office Action again reiterates the previous assertion that Bacus "teaches a method for determining the effectiveness of a therapeutic agent in the treatment of cancer," because Bacus teaches obtaining a *single* biopsy from a human having cancer, dividing the biopsy into two proteins, treating one of the two portions *in vitro* with a compound, and comparing the percentage of cells that exhibit markers of terminal differentiation in both portions after allowing both portions to grow *in vitro*. Important distinctions between the pending claims and the Bacus reference are ignored in this analysis. For example, the instant claims require a comparison of two separate samples, obtained at separate times, both before and after treatment has occurred; in contrast, Bacus teaches the skilled worker to obtain one sample before treatment to be divided and differentially treated. By ignoring this difference, the Office Action fails to appreciate that, in contrast to Bacus, the sample obtained using the instantly-claimed methods are *different* samples, *i.e.*, the prior art explicitly teaches away from this positively-recited limitation in the pending claims.

The Office Action asserts that such an argument is not persuasive, dismissing Applicant's argument by stating that "if the teaching of Bacus were the same as that of the instant claims, the rejection would have been made under 35 U.S.C. 102 rather than 103." *Office Action* at 10. The Office Action is apparently arguing that an analysis of the differences between the pending claims and Bacus is irrelevant. However, this argument fails to take into account that the comparison between Bacus and the present invention is but one step of the obviousness

determination. In fact, the Supreme Court has dictated that it is necessary to ascertain the differences between the prior art and the claims at issue. *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966). Thus, it is not irrelevant to consider the differences between Bacus and the claims at issue.

Instead, the Office Action asserts that "the difference between Bacus and the instant claims" has previously been addressed and summarily concludes that the claimed invention has "'a direct correspondence with the method of Bacus.'" The only explanation offered for this conclusion is that Bacus is analogous to the instantly claimed methods – "'wherein the first sample is the control because the individual with the tumor has not yet been exposed to the therapeutic agent and the second sample is after exposure to the therapeutic agent corresponding to a sample obtained from an individual after exposure to the agent *in vivo*.'" *Office Action* at 10. However, the Office Action fails to address Applicant's position that it is not clear that the skilled worker would have any confidence that a method using a single sample obtained at a specific time during the course of an illness (such as cancer), which is split and then treated under laboratory-controlled conditions *in vitro* using defined (and continuously-variable) concentrations of specific chemotherapeutic drugs, could give rise to an reasonable expectation that methods using different samples obtained at different times and from different point in the course of an illness (such as cancer), and after treatment *in vivo* with a chemotherapeutic agent having variable and indeterminate concentrations at the sampling site would be successful. For example, a biological sample that is passaged *in vitro* inevitably becomes less heterogeneous as stromal cells fail to proliferate under these experimental conditions. On the other hand, treatment of a subject *in vivo* with a chemotherapeutic agent will have variable and indeterminate concentrations at the sampling site and indeterminate periods of contact of the agent at said site,

and in fact analysis performed on different samples, even if taken from the same site, will show variable levels of tissue heterogeneity.

Instead, the Office Action declares (incorrectly) that "Applicant does not provide arguments of why in the case of the *in vitro* method of Bacus, there would be no reasonable expectation of success" for the present invention. *Id.* at 11. At the same time, the Office Action makes the bald assertion that one of skill in the art "would always" be motivated to extend *in vitro* methods of treating tumor cells to *in vivo* methods, "*as long as there was reasonable expectation of success.*" *Office Action* at 10-11 (emphasis added). However, rather than provide examples of why a skilled artisan would have a *reasonable expectation of success*, the Office Action instead explains that the *motivation* to test chemical agents on cells *in vitro* is solely for the future treatment of an individual. Of course, demonstration of motivation "for finding chemical agents which selectively induce cell death of tumor cells" is irrelevant for the present claims drawn to methods for determining a response to administration of a chemotherapeutic or chemopreventive agent to an individual. Notwithstanding this fact, there is no evidence provided whatsoever that a skilled artisan would have a reasonable expectation of success of extending *in vitro* methods of treating tumor cells to *in vivo* methods, even if there was such actually motivation to do so.

Rather, the Office Action makes three unbelievable (and untenable) observations regarding Applicants previous responses; (1) that the Patent Office would accept an *in vitro* method to provide enablement for an *in vivo* method, *provided there was no information to the contrary* (such as scientific reasoning indicating why there would *not* be a reasonable expectation of success, or supporting undue experimentation); (2) that it is the applicant's responsibility to establish a prima facie case of non-obviousness; and (3) that in making an obviousness rejection,

the claimed invention need not be treated as a whole. Each of these observations will be addressed in turn.

As for the observation regarding *in vitro* methods providing enablement for *in vivo* methods, Applicants previously provided an abundance of case law from the Federal Circuit and the Board of Patent Appeals and Interferences (the "Board") regarding situations where *in vitro* results were not predictive of *in vivo* efficacy. For example, in a case where there were published reports of *in vitro* bactericidal activity of a compound, the Federal Circuit noted that "simply because a drug gives positive results *in vitro*, it does not necessarily follow that there is a reasonable probability of success for therapeutic use of the drug *in vivo*." *In re Gangaharam*, 13 U.S.P.Q.2d 1568, 1570 (Fed. Cir. 1989) (unpublished). On the subject of using *in vitro* screening tools to identify anti-viral compounds, the Board concluded that "[w]hile the *in vitro* testing performed on these anti-viral compounds appears to be useful as a screening tool in order to determine which of these anti-viral compounds are *candidates* for further testing to determine if they possess *in vivo* utility, the *in vitro* tests were not predicative of *in vivo* efficacy." *In re Balzarini*, 21 U.S.P.Q.2d 1892 (B.P.A.I. 1991). The Office Action dismissed all of the case law cited by Applicant, stating that *all* of the cases presented had different facts to those of the present case because the cited cases turned on "an isolated property of a novel substance *in vitro* [that] was relied upon for enablement for [sic] efficacy *in vivo*."

The Office Action position is apparently that the rejection in the present case was not based on an unknown compound that could be screened by Bacus, but rather that the "combinations of known anti-tumor drugs, already recognized in the art as having anti-tumor effects, would have a reasonable expectation of success *in vivo*." *Office Action* at 17. This conclusion focuses too intently on the differences between *in vivo* and *in vitro* results, and

completely ignores the actual subject matter of the present invention. In fact, the present invention is not drawn to methods that utilize known combinations of anti-tumor drugs, let along any other treatment methods, but rather methods of measuring expression of the biological markers p21, p27, p16, TGF-ß, and SA-ß-Gal in tissue or cell samples from an individual both before and after treatment with an agent and using those results to determine if the individual responded to treatment. As such, the present invention is concerned with determining whether an individual actually responded to treatment with a chemotherapeutic or chemopreventive agent by measuring one or more of p21, p27, p16, TGF-ß, and SA-ß-Gal. Therefore, all evidence presented in the Office Action to establish that a skilled artisan would be motivated to use compound *in vivo* that were screen *in vitro* are irrelevant.

In fact, Applicant continued by posing the hypothetical question of the reverse situation – whether an applicant would receive favorable consideration by the Patent Office if proposing to extend *in vitro* methods to claim *in vivo* efficacy. The unexpected response to this inquiry was that "without information to the contrary, (i.e., scientific reasoning indicating why there would not be reasonable expectation of success or scientific reasoning supporting undue experimentation) an *in vitro* method would indeed provide enablement and motivation for an in vitro method. However, Applicant notes that the case law and the internal guidelines of the Patent Office do not support this position. Instead, an "Examiner is required to weigh the evidence for and against correlation [between *in vitro* assays and claimed method] and decide whether one skilled in the art would accept the model as reasonably correlated to the condition." M.P.E.P. 2164.02 (*citing In re Brana*, 51 F.3d 1560, 1566 (Fed. Cir. 1995). In this case, there is just no evidence that a skilled artisan would accept that analyzing cells removed from an

individual both before and after treatment would correlate to analyzing cells that were instead treated *in vitro*.

As for the second observation, the Office Action appears to suggest that the Applicant must establish a *prima facie* case of non-obviousness. The Office Action faults Applicant for not providing "arguments of why in the case of the *in vitro* method of Bacus, there would be no reasonable expectation of success." *Office Action* at 11. Notwithstanding the fact that Applicant provided substantial support for the proposition that there would have been no reasonable expectation of success in previous responses, the burden for establishing the *prima facie* case is clearly on the Examiner – a burden that was not only not met, but was never actually addressed. According to the Patent Office's owns procedures, "the examiner bears the initial burden of factually supporting any *prima facie* conclusion of obviousness." M.P.E.P. § 2142. In fact, "[i]f the examiner does not produce a *prima facie* case, the applicant is under *no obligation* to submit evidence of nonobviousness." *Id.* There are three basic criteria that must be met to establish a *prima facie* case of obviousness; (1) there must some suggestion or motivation to modify the reference or to combine reference teachings, (2) *there must be a reasonable expectation of success*, and (3) the prior art references must teach or suggest all of the claim limitations. *Id.* (emphasis added). Instead of providing evidence of the second criteria, however, the Office Action continued to provide more reasons why there would be a motivation to combine the references. Because the Office Action never even addressed why there would have been a reasonable expectation of success at arriving at the claimed invention, and even though Applicant has consistently provided evidence to the contrary, Applicant has never been under an obligation to do so.

As for the final observation, the Office Action apparently asserts that it is not necessary to determine if the claimed invention as whole would have been obvious. The Office Action provided no response to our previous assertion on this point. *Office Action* at 11. Moreover, in response to Applicant's previous assertion that the previous Office Action improperly focused on whether it would have been obvious to treat individuals with an agent known to be effective for the treatment of cells in culture rather than a method of prognosticating the effectiveness of a therapeutic agent by removing a biopsy sample from an individual before and after the treatment (in fact, similar to Applicant's assertion above), the Office Action pointed out that this was not persuasive because the "last active method step in claim 1 requires the determining if a biological maker associated with apoptosis was increased following exposure to the chemotherapeutic agent." *Id.* at 12. The Office Action proceeds to cite to Bacus at length, concluding that it is clear that "the determination of the effectiveness of cancer therapy taught be Bacus is the same as determining a response to administration of a chemotherapeutic agent to an individual." However, this is akin to distilling the claimed invention down to the "gist" or "thrust" of the invention, which disregards the requirement of analyzing the subject matter "as a whole." M.P.E.P. § 2142.02 (*citing W.L. Gore & Assoc., Inc. v. Garlock, Inc.*, 721 F.2d 1540 (Fed. Cir. 1983)). Applicant asserts that the Office Action has improperly analyzed the invention, focusing on the gist of the invention, rather than determining whether the invention as a whole would have been obvious. As such, the analysis should not be whether it is obvious to merely determine a response to an agent *in vivo*, but rather would it have been obvious to do what is instantly claimed: measure expression of one or more of the biological markers p21, p27, p16, TGF-ß, and SA-ß-Gal in tissue or cell samples from an individual both before and after treatment with an agent and using those results to determine if the individual actually responded to treatment.

The deficiencies of Bacus are not overcome by the combination with the other cited art. Smith describes the use of primary chemotherapy in breast cancer treatment. The Office Action cites the abstract of Smith for the proposition that neoadjuvant chemotherapy is a rapidly evolving area in the management of early operable breast cancer, achieving significant responses around 80% of patients with the concomitant reduction in the necessity of mastectomy. The Office Action also cites the abstract of Smith for the proposition that neoadjuvant chemotherapy allows for serial biological measurements of treated breast cancers, which may aid in the selection of appropriate treatment of individual patients an allow the rapid assessment of new therapies. However, the abstract of Smith merely states that primary chemotherapy allows the use of serial biological measurements of treated breast cancers. Instead, Smith actually only describes the observation of morphological characteristics of cells that have undergone apoptosis (*i.e.*, the apoptotic index). As such, Smith certainly does not teach a method for determining a response to administration of a chemotherapeutic or chemopreventive agent to an individual by measuring one of more of the biological markers p21, p27, p16, TGF-ß, and SA-ß-Gal, much less measuring the optical density of cells after immunohistochemically staining them with a detectably labeled antibody directed against such biological markers.

Porter, Los, and Barbara-Guillem are all individually cited by the Office Action as teaching the monitoring of therapeutic effectiveness of chemotherapy in a mammal comprising administering a therapeutic agent, performing a biopsy of the tumor, and detecting the *in vitro* level of a marker in the tumor cells as indicative of clinical response to the therapeutic agent. Porter describes the measurement of determinants related to the *in vivo* induction of spermidine/spermine N-acetyltransferase subsequent to polyamine analog treatment. Los describes the use of the GADD153 gene as a molecular marker for *in vivo* tumor cell injury that

occurs in response to chemotherapy. Barbara-Guillem describes using the measurement of cell-associated interleukin-2 receptor α expression in aiding the monitoring of efficacy of anticancer therapy against metastatic cells of non-lymphoid tumors. However, even if Porter, Los, and Barbara-Guillem describe collecting a biological sample after administration of a chemotherapeutic or chemopreventive agent, none of these references teach, much less suggest, collecting a sample from an individual before exposure to the agent. Further, neither Porter, Los, and Barbara-Guillem teach methods whereby a response to a chemotherapeutic or chemopreventive agent is determined by immunohistochemically measuring the optical density of a cell stained with a detectably labeled antibody directed against one or more of the biological markers p21, p27, p16, TGF-ß, and SA-ß-Gal.

Applicants respectfully contend that the Office Action has failed to establish a *prima facie* case of obviousness because first, there is no teaching, suggestion or motivation to combine the cited references, and second, even if the references are improperly combined, all of claim limitations are not taught or suggested by the combination of Bacus I, Smith, Porter, Los, or Barbera-Guillem. The Office Action argues that it would have been obvious to determine the effectiveness of a therapeutic agent in the treatment of cancer by measuring the ability of the therapeutic agent to induce terminal differentiation by means of a) obtaining a sample of cells or tissues from the patient before chemotherapy and obtaining a second sample of cells or tissues from said patient after chemotherapy; b) quantitating the presence of Her-2/neu on the surface of said cells by means of an antibody labeled with a fluorophore or a chromogen; c) quantitating the total number of cells by staining DNA; and d) subjecting the cells to image analysis so that a percentage of cells expressing both labeled antibody and labeled DNA can be quantified in order to measure the effectiveness of combined therapy in the induction of apoptosis in breast cancer

cells in patients having undergone therapy. Further, the Office Action argues that a skilled artisan would have been motivated to do so with a reasonable expectation of success by teachings of Bacus regarding the targeting of stabilization and reduction of a cell population by means of terminal differentiation in a method of treating breast cancer and the teaching of the abstract of Smith on the serial biological measurements of treated breast cancer *in vivo* to determine if the treatment was appropriate for the individual patient, supplemented with the teachings of any of Porter, Los, or Barbera-Guillem on the *in vivo* monitoring of therapeutic efficacy by assaying a sample taken from a patient after administration of a therapeutic agent. However, the mere description in Bacus of using image analysis to *predict* whether a chemotherapeutic agent would be effective for a patient does not amount to a teaching or suggestion to determine or monitor a *response* of an individual to the administration of a chemotherapeutic agent. The secondary references do not cure this infirmity. Smith may describe the measurement of morphological characteristics of treated breast cancers, and Porter, Los, and Barbera-Guillem may individually teach that assaying a sample taken from a patient after administration of a therapeutic agent, but none of these references teach immunohistochemically staining two samples removed from an individual, both before and after exposure to the treatment, and measuring the optical density of the stained cells. In the absence of such teaching, Applicants contend there was simply no motivation to combine these references as the Office Action suggests.

Moreover, the mere fact that individual references *can* be combined does not render the resultant combination obvious *unless* the prior art also suggests the desirability of the combination. *In re Mills*, 916 F.2d 680; 16 USPQ2d 1430 (Fed. Cir. 1990). Therefore, although the prior art may be capable of being combined or modified, there *must* be a suggestion or motivation in the reference to do so. *In re Mills*, 916 F.2d at 682; see also *In re Fritch*, 972 F.2d

1260 (Fed. Cir. 1992); M.P.E.P. § 2143.01. Moreover, even if the references relied upon teach that aspects of the claimed invention were individually known in the art, this alone is not sufficient to establish a *prima facie* case of obviousness, without some objective reason (outside the teachings of Applicants' specification) to combine the teachings of the references. *Ex parte Levengood*, 28 USPQ2d 1300 (Bd. Pat. App. & Inter. 1999); M.P.E.P. § 2143.01.

In fact, the Federal Circuit "has recently reemphasized the importance of the motivation to combine . . . ." *Yamanouchi Pharm. Co. v. Danbury Pharmacal, Inc.*, 231 F.3d 1339, 1343, 56 USPQ2d 1641, 1644 (Fed. Cir. 2000). In making a 35 U.S.C. § 103(a) determination, "[o]bviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teachings, suggestion, or incentive supporting the combination." *In re Greiger*, 815 F.2d 686, 688, 2 USPQ2d 1276, 1278 (Fed. Cir. 1987). Also, "'broad conclusory statements regarding the teaching of multiple references, standing alone, are not evidence'[of obviousness]" *Ecolochem, Inc. v. S. Calif. Edison Co.*, 227 F.3d 1361, 1372, 56 U.S.P.Q.2d 1065, 1073 (Fed. Cir. 2000) (quoting *In re Dembiczak*, 175 F.3d 994, 999, 50 U.S.P.Q.2d 1614, 1617 (Fed. Cir. 1999)).

A more recent decision by the Federal Circuit further dictates that the teaching, motivation, or suggestion to combine *cannot* be based solely on the "common knowledge and common sense" of a skilled artisan, but rather must be based on the evidence found in the record. *In re Lee*, 61 U.S.P.Q.2d 1430 (Fed. Cir. 2002). Thus, if the reason to combine is common and well known, the Office should be able to cite a reference establishing that fact. Accordingly, "to establish obviousness based on a combination of the elements disclosed in the prior art, there *must* be some motivation, suggestion, or teaching of the desirability of making the specific combination that was made by the applicant," to one of ordinary skill in the art. *In re Kotzab*,

217 F.3d 1365, 1370, 55 U.S.P.Q.2d 1313, 1316 (Fed. Cir. 2000) (*emphasis added*). In addition, "'the showing of combinability must be clear and particular.'" *Ruiz v. A.B. Chance Co.*, 234 F.3d 654, 665, 57 U.S.P.Q.2d 1161, 1168 (Fed. Cir. 2000) (quoting *Dembiczak*, 175 F.3d at 999, 50 U.S.P.Q.2d at 1017).

Applicant respectfully submits that the Office Action has engaged in impermissible hindsight to support its argument. In this regard, the Federal Circuit dictates, "[i]t is impermissible to use the claimed invention as an instruction manual or 'template' to piece together the teachings of the prior art so that the claimed invention is rendered obvious. This court has previously stated that '[o]ne cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention." *In re Fritch*, 23 U.S.P.Q.2d 1780, 1784 (Fed Cir. 1992) (citations omitted) (quoting *In re Fine*, 5 U.S.P.Q.2d 1596, 1600 (Fed. Cir. 1988)); *see also Para-Ordnance Mfg., Inc. v. SGS Imposters Int'l Inc.*, 37 U.S.P.Q. 1237, 1239 (Fed. Cir. 1995) ("Obviousness may not be established using hindsight or in view of the teachings or suggestions of the inventor."); *Heidelberger Druckmaschinen AG v. Hantscho Commercial Prods. Inc.*, 30 U.S.P.Q.2d 1377 (Fed. Cir. 1993) ("The motivation to combine references cannot come from the invention itself."); *Interconnect Planning Corp. v. Feil*, 227 U.S.P.Q. 543, 547 (Fed. Cir. 1985) ("The invention must be viewed not with the blueprint drawn by the inventor, but in the state of the art that existed at the time."). Applicants respectfully submit that what the law precludes is precisely the basis for the asserted obviousness rejection.

For the reasons set forth above, none of the references cited in support of this ground of rejection, specifically Bacus, Smith, Porter, Los, and Barbera-Guillem, taken either alone or in any combination, disclose, either individually or in combination, a method for determining a

response to administration of a chemotherapeutic or chemopreventive agent to an individual according to the claimed methods. Accordingly, Applicant respectfully requests withdrawal of this rejection and requests reconsideration of the claims.

Claims 1-3 , 5, and 6 are rejected under 35 U.S.C. § 103(a) as being unpatentable for obviousness over Bacus in view of the abstract of Smith, and any of Porter, or Los, or Barbera-Guillem (all cited above) and further in view of the abstract of Vollmer *et al.* (Cancer Research, 1992, Vol. 52, pp. 4642-4648) ("Vollmer"), and the abstract of Dannecker *et al.* (Ann. Oncol., 1996, Vol. 7, pp. 391-395) ("Dannecker"), and the abstract of Kopp *et al.* (Cancer Research, 1995, Vol. 55, pp 4512-4515) ("Kopp"). Applicant respectfully traverses this rejection.

As above, Applicant notes that the Office Action improperly cites to the abstracts of Smith, Vollmer, Dannecker, and Kopp, rather than the underlying full text document, to support this obviousness rejection, contrary to the internal guidelines of the Patent Office. M.P.E.P. 706.02(II). Applicant submits the underlying full text document of Smith, Vollmer, Dannecker, and Kopp with this Response and respectfully requests they be given thorough consideration and that they be cited of record in the prosecution history of the present application.

The deficiencies of several of these references (Bacus, Smith, Porter, Los, and Barbera-Guillem) in supporting an obviousness rejection of these claims has been set forth above, and applies with equal force with regard to this separately-enunciated ground of rejection and will not be repeated here except by reference. None of the additionally-cited references, taken alone or in any combination with the earlier-discussed references, teach or suggest the instantly claimed method. The deficiencies of Bacus, the abstract of Smith, Porter, Los, and Barbera-Guillem are not overcome by the combination with the other cited art.

Vollmer discloses that studies on tenascin expression were conducted by comparative immunolocalization of tenascin in sections of rat mammary tumors that had undergone various treatments, including treatment with antiprogestin. Vollmer is cited in the Office Action as allegedly teaching that antiprogestins inhibit tumor growth by induction of terminal differentiation. Dannacker describes that the antiprogestin onapristone has varying effects on TGF-beta secretion in breast cancer cell *in vitro*. The abstract of Dannacker is cited in the Office Action for allegedly teaching that the antiproliferative action of an antiprogestin increased TGF-beta secretion by breast tumor cells, and that one skilled in the art would reasonably conclude that the induction of terminal differentiation in breast tumor cells results in the secretion of TGF-beta by said cells. The abstract of Kopp discloses that the blood levels of TGF-beta 2 increased in breast cancer patients that responded to receiving treatment with the antiestrogen tamoxifen. The Office Action cites the abstract of Kopp as teaching that plasma levels of TGF-beta are increased in the first 2 to 6 weeks in breast cancer patients having undergone treatment with tamoxifen and experiencing remission. However, neither Vollmer, Dannacker, nor Kopp teach, much less suggest, the instantly claimed invention.

Thus, Applicant respectfully submits that the Office Action has failed to establish a *prima facie* case of obviousness against the rejected claims, *inter alia*, because all of the claim limitations are not taught or suggested by the combination of the cited references. The Office Action argues that it would have been obvious to one of ordinary skill to measure the degree of terminal differentiation induced by the translocation of HER-2/*neu* by measuring the TGF-beta in the blood plasma before and after administration of an anti-HER-2/*neu* antibody. Further, the Office Action argues that a skilled artisan would have been motivated to do so with a reasonable expectation of success by the teachings of the abstracts of Vollmer and Dannecker which link the

induction of terminal differentiation with TGF-beta secretion in breast tumor cells, and the abstract of Kopp which teaches that plasma level of TGF-beta are markedly higher in breast cancer patients having undergone remission due to treatment. The Office Action even acknowledges that it cites the abstracts of Vollmar, Dannecker, and Kopp because of the apparent deficiency in Bacus, and the abstract of Smith, Porter, Los, and Barbera-Guillem as not teaching the biological markers of p21, p27, p16, TGF-beta, or SA-Beta-Gal. *Office Action* at 5. Thus, the abstracts of Vollmar, Dannecker, and Kopp are cited as establishing "that the secretion of TGF-beta upon induction of terminal differentiation by antiprogestins would be measurable in the blood plasma of a patient." This apparent connection is then used to support the supposition that a skilled artisan "would expect that breast cancer patients who undergo remission by the induction of terminal differentiation by administration of the anti-HER-2/*neu* antibody taught by Bacus would exhibit marked increase in blood plasma levels of TGF-beta, because this was demonstrated for the therapeutic agent tamoxifen." The Office Action, however, fails to cite any evidence that would establish that treatment with anti-HER-2/*neu* antibody would have the same or similar effects as treatment with tamoxifen, or indeed have any effect on the expression levels of TGF-beta, much less that there would be a comparable increase in blood plasma levels of TGF-beta as seen after treatment with tamoxifen when breast cancer patients are treated with anti-HER-2/*neu* antibody. Regardless, in view of the fact that combination of Vollmar, Dannecker, and Kopp at best are solely concerned with identifying levels of TGF-beta in the blood as a biomarker of breast cancer patients undergoing remission after treatment with a compound, the references add nothing to the fatally-defective teachings of Bacus, Smith, Porter, Los, and Barbera-Guillem, and by themselves do not teach or suggest immunohistochemically staining two samples removed from an individual, both before and after exposure to the

treatment, and measuring the optical density of the stained cells. In the absence of such teaching, Applicants contend there was simply no motivation to combine these references as the Office Action suggests. Once again, it is Applicant's position that the obviousness rejection based on this combination of references in the Office Action has been achieved through the use of impermissible hindsight, and that the pending claims are non-obvious over the cited art, taken alone or in any combination.

For the reasons set forth above, Bacus, Porter, Los, Barbara-Guillem, and Vollmer, Dannecker, or Kopp do not disclose, either individually or in combination, nor render obvious the claimed methods for determining a response to administration of a chemotherapeutic or chemopreventive agent to an individual. Accordingly, Applicant respectfully requests that the Examiner withdraw this ground of rejection and pass these claims to issue.

Claims 1-6 are rejected under 35 U.S.C. § 103(a) as being unpatentable for obviousness over Bacus in view of the abstract of Smith, and any of Porter, or Los, or Barbera-Guillem (all cited above) and further in view of the abstracts of Vollmer, Dannecker, Kopp (all cited above), and further view of Dash. (U.S. Patent 5,772,998). Applicant respectfully traverses this rejection.

Again, Applicant notes that the Office Action improperly cites to the abstracts of Smith, Vollmer, Dannecker, and Kopp, rather than the underlying full text document, to support this obviousness rejection, contrary to the internal guidelines of the Patent Office. M.P.E.P. 706.02(II). Applicant submits the underlying full text document of Smith, Vollmer, Dannecker, and Kopp with this Response and respectfully requests they be given thorough consideration and that they be cited of record in the prosecution history of the present application.

The deficiencies of several of these references (Bacus, Smith, Porter, Los, Barbera-Guillem, Vollmer, Dannecker, and Kopp) in supporting an obviousness rejection of these claims has been set forth above, applies with equal force with regard to this separately-enunciated ground of rejection and will not be repeated here except by reference. The only additional reference, Dash, is cited as teaching a method for diagnosing a disease or disorder such as cancer using a capture-ELISA method for quantitating the concentration of TGF-beta in a biological sample. However, Applicant has never indicated that antibodies to TGF-beta, or methods of using them, did not exist prior to the present invention. Indeed, the invention is not drawn to any specific antibodies, but rather to methods for determining a response to administration of a chemotherapeutic or chemopreventive agent to an individual. And, Dash does not teach that the disclosed antibody can be used for determining a *response* to administration of a chemotherapeutic or chemopreventative agent, much less teach or suggest that such an antibody could be used in a method of the claimed invention (which methods are also nowhere disclosed in this or any other of the cited references). As such, Dash is irrelevant to the obviousness determination of the present invention.

For the reasons set forth above, Bacus, Smith, Porter, Los, Barbara-Guillem, Vollmer, Dannecker, Kopp, and Dash do not disclose, either individually or in combination, nor render obvious the claimed methods for determining a response to administration of a chemotherapeutic or chemopreventive agent to an individual. Accordingly, Applicant respectfully requests that the Examiner withdraw this ground of rejection and pass these claims to issue.

Claims 1-3, 5 and 6 are rejected under 35 U.S.C. § 103(a) as being unpatentable for obviousness over Bacus in view of Smith, and any of Porter, or Los, or Barbera-Guillem (all

cited above) and further in view of the abstracts of Warri (J. Nat'l Cancer Inst., 1993, vol. 85, pp. 1412-1418) ("Warri"), Sasaki (Jpn J. Cancer Res., 1998, vol. 89, pp.562-570) and the abstract of Srivastava (Anticancer Res., 1998, vol. 18, pp. 4003-4010). Applicant respectfully traverses this rejection.

Once again, Applicant notes that the Office Action improperly cites to the abstracts of Smith, Warri, and Srivastava, rather than the underlying full text document, to support this obviousness rejection, contrary to the internal guidelines of the Patent Office. M.P.E.P. 706.02(II). Applicant submits the underlying full text document of Smith, and Srivastava with this Response and respectfully requests they be given thorough consideration and that they be cited of record in the prosecution history of the present application. Further, Applicant notes that the underlying full text document of Warri was cited in a previous Office Action. Applicant respectfully requests that the underlying full text document of Warri be given thorough consideration for this separate ground of rejection.

The deficiencies of several of these references (Bacus, Smith, Porter, Los, and Barbera-Guillem) in supporting an obviousness rejection of these claims has been set forth above, and applies with equal force with regard to this separately-enunciated ground of rejection and will not be repeated here except by reference. None of the additionally-cited references, taken alone or in any combination with the earlier-discussed references, teach or suggest the instantly claimed method. The deficiencies of Bacus, Smith, Porter, Los, and Barbera-Guillem are not overcome by the combination with the other cited art.

The Office Action acknowledges that none of the previously cited references "teaches a biological marker associated with apoptosis." *Office Action* at 7. The Office Action continues then to make the unsupported assertion that apoptosis is included within the definition of

terminal differentiation of Bacus, because Bacus refers to terminal differentiation as "the stabilization and reduction of a cell population," and that apoptosis results in said stabilization and reduction of a cell population. *Id.* Applicant respectfully disagrees with the Office regarding this assertion. However, solely in an effort to expedite the allowance of the claims, Applicant has amended the instant claims, rendering this argument moot as to these claims.

Warri describes the use of Toremifene, an antiestrogen, to cause growth inhibition of estrogen-sensitive breast cancer cells by inducing some cells to under apoptosis and by inhibiting other cells from entering mitosis. The Office Action cites Warri for the proposition that methods for treating breast cancer *should* target the induction of apoptosis to breast cancer cells, even though the actual conclusion of Warri is only that apoptosis "provides a *potential* new therapeutic approach for treating breast cancer." Warri is also cited as teaching the up-regulation of expression of TGF-beta after treatment with an anti-estrogen compound which causes apoptosis in breast cancer cells. Nevertheless, Warri does not teach or suggest the claimed methods for collecting both a first and second tissue or cell sample from an individual, both before and after exposing the individual to a chemotherapeutic or chemopreventative agent, and measuring the optical density of cells after immunohistochemically staining them with a detectably labeled antibody directed against one or more of the biological markers p21, p27, p16, TGF-ß, or SA-ß-Gal.

Sasaki is cited as teaching that an anti-ERB2 antibody CH401, which allegedly inhibited tumor growth by the induction of apoptosis. The abstract of Srivastava is cited as teaching TGF-beta and p21 are apoptotic genes in human breast cells. However, neither Sasaki nor Srivastava teach that the disclosed information could be used for determining a response to administration of a chemotherapeutic or chemopreventative agent, much less teach or suggest that such

information could be used in a method of the claimed invention (which methods are also nowhere disclosed in this or any other of the cited references).

Thus, Applicant respectfully submits that the Office Action has filed to establish a *prima facie* case of obviousness against the rejected claims, *inter alia*, because all of the claim limitations are not taught or suggested by any combination of Bacus, Smith, Porter, Los, and Barbera-Guillem, and further in view of Warri, Sasaki, and Srivastava. The Office Action argues that it would have been obvious to one of ordinary skill to evaluate a patients response to chemotherapy comprising the administration of the anti-ERB2 antibody, CH401, by means of obtaining a biological sample before treatment and after treatment, and quantitating the induction of apoptosis by means of a labeled anti-p21 antibody or a labeled anti-TGF-beta antibody, quantitating the total number of cells by staining DNA, and subjecting labeled cells to image analysis such that a percentage of cells expressing both labeled antibody and labeled DNA can be quantified in order to measure the effectiveness of anticancer therapy by measuring the induction of apoptosis in breast cancer cells in patients having undergone therapy. Further, the Office Action argues that a skilled artisan would have been motivated to do so with a reasonable expectation of success by the teachings of Warri on the targeting of apoptosis to breast cancer cells as a therapeutic approach for treating breast cancer, the teaching of Sasaki on the CH401 antibody, the teaching of the abstract of Srivastava for identifying TGF-beta and p21 as genes which are expressed during apoptosis of breast cells, and the teachings of Bacus, on the targeting of stabilization and a reduction of a cell population in a method of treating breast cancer. However, for reasons set out above, Bacus, Smith, Porter, Los, and Barbera-Guillem do not teach or suggest a method for determining or monitoring a response of an individual to the administration of a chemotherapeutic or chemopreventive agent by measuring the optical density

of cells after immunohistochemically staining them with a detectably labeled antibody directed against one or more of the biological markers p21, p27, p16, TGF-ß, or SA-ß-Gal. Because Warri and Sasaki are merely concerned with describing specific treatments of breast cancer by targeting apoptosis, and Srivastava merely describes specific biological markers for apoptosis of breast cells, they do not contemplate a method for determining or monitoring a response using those specific treatments, or by monitoring those specific antibodies, much less a method of the present invention. In the absence of such teaching, there was simply no motivation to combine these references, as the Office Action suggests. Once again, it is Applicant's position that the obviousness rejection based on this combination of references in the Office Action has been achieved through the use of impermissible hindsight and that the pending claims are non-obvious over the cited art, taken alone or in any combination.

For the response set forth above, Bacus, Smith, Porter, Los, Barbera-Guillem, Warri, Sasaki, and Srivastava do not disclose, either individually or in combination, a method for determining a response to administration of a chemotherapeutic or chemopreventive agent to an individual. Accordingly, Applicant respectfully requests withdrawal of this rejection and requests reconsideration of the claims.

Claims 1-3, 5 and 6 are rejected under 35 U.S.C. § 103(a) as being unpatentable for obviousness over Bacus in view of the abstract of Smith, and any of Porter, or Los, or Barbera-Guillem (all cited above) and further in view of the abstracts of the abstract of Gillett *et al.* (J. Pathol., 1999 Jan., 187(2):200-6) and the abstract of Emig *et al.* (Br. J. Cancer, 1998, Vol. 78, pp. 1661-1668). Applicant respectfully traverses this rejection.

Again, Applicant notes that the Office Action improperly cites to the abstracts of Smith, Gillett and Emig, rather than the underlying full text document, to support this obviousness rejection, contrary to the internal guidelines of the Patent Office. M.P.E.P. 706.02(II). Applicant submits the underlying full text document of Smith, Gillett and Emig with this Response and respectfully requests they be given thorough consideration and that they be cited of record in the prosecution history of the present application.

The deficiencies of several of these references (Bacus, Smith, Porter, Los, and Barbera-Guillem) in supporting an obviousness rejection of these claims has been set forth above, applies with equal force with regard to this separately-enunciated ground of rejection and will not be repeated here except by reference. None of the additionally-cited references, taken alone or in any combination with the earlier-discussed references, teach or suggest the instantly claimed method. The deficiencies of Bacus, the abstract of Smith, Porter, Los, and Barbera-Guillem are not overcome by the combination with the other cited art.

The Office Action acknowledges that Bacus, Smith, Porter, Los, and Barbera-Guillem do not teach p27 or p16 as biological marker proteins associated with terminal differentiation or apoptosis. The abstract of Gillett is cited as teaching that low levels of p27 were observed in high grade, rapidly proliferating breast tumors. However, Gillett also teaches that when using multivariate analysis, "p27 was not an independent predictor of survival when either histological grade or proliferative activity is included in the model." Therefore, Gillett actually teaches away from using p27 as an indicator of prognosis. The abstract of Emig is cited as teaching antibodies to human p16 can be used in immunohistochemical analysis to monitor the expression of p16 in breast cancer cells. However, Emig does not teach the effects of any chemotherapeutic or chemopreventive agent. In any event, neither Gillett nor Emig teach a method of collecting both

a first and second tissue or cell sample from an individual, both before and after exposing the individual to a chemotherapeutic or chemopreventive agent, and measuring the optical density of cells after immunohistochemically staining them with a detectably labeled antibody directed against one ore more of the biological markers p21, p27, p16, TGF-beta, and SA-Beta-Gal.

Thus, Applicant respectfully submits that the Office Action has failed to establish a *prima facie* case of obviousness against the rejected claims, *inter alia*, because all of the claim limitations are not taught or suggested by Bacus, Smith, Porter, Los, and Barbera-Guillem, and further in view of Gillett and Emig. The Office Action argues that it would have been obvious to one of ordinary skill to measure p16 and p27 as negative markers or terminal differentiation in the method allegedly rendered obvious by Bacus, the abstract of Smith, Porter, Los, and Barbera-Guillem. Further, the Office Action argues that a skilled artisan would have been motivated to do so with a reasonable expectation of success by the teachings of the abstracts of Gillette and Emig that correlated low levels of p27 with rapidly proliferating breast cells and aberrant expression of p16 with rapidly proliferating breast cells. However, for reasons set out above, Bacus, Smith, Porter, Los, and Barbera-Guillem do not teach or suggest a method for determining or monitoring a response of an individual to the administration of a chemotherapeutic or chemopreventive agent by measuring the optical density of cells after immunohistochemically staining them with a detectably labeled antibody directed against one or more of the biological markers p21, p27, p16, TGF-ß, or SA-ß-Gal. Further, because Gillette and Emig are merely concerned with describing specific biological markers for breast cells, they do not contemplate a method for determining or monitoring a response using those specific treatments, or by monitoring those specific antibodies, much less a method of the present invention. In the absence of such teaching, there was simply no motivation to combine these

references, as the Office Action suggests. Once again, it is Applicant's position that the obviousness rejection based on this combination of references in the Office Action has been achieved through the use of impermissible hindsight and that the pending claims are non-obvious over the cited art, taken alone or in any combination.

For the response set forth above, Bacus, Smith, Porter, Los, Barbera-Guillem, Gillett and Emig do not disclose, either individually or in combination, a method for determining a response to administration of a chemotherapeutic or chemopreventive agent to an individual. Accordingly, Applicant respectfully requests withdrawal of this rejection and requests reconsideration of the claims.

Discussion of the Obviousness-type Double Patenting Rejection(s)

Claims 1, 2, 5, and 6 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Bacus in view of the abstract of Smith and al-Mounhri (Biomed. Pharmacother., 1998, Vol. 52, pp. 116-121) ("Smith") and any of Porter (U.S. 5,498,522) ("Porter") or Los *et al.* (U.S. 6,447,997) ("Los") or Barbera-Guillem *et al.* (U.S. 5,536,642) ("Barbera-Guillem"). Further, Claims 1-3 , 5, and 6 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Bacus in view of the abstract of Smith, and any of Porter, or Los, or Barbera-Guillem (all cited above) and further in view of the abstract of Vollmer *et al.* (Cancer Research, 1992, Vol. 52, pp. 4642-4648) ("Vollmer"), and the abstract of Dannecker *et al.* (Ann. Oncol., 1996, Vol. 7, pp. 391-395) ("Dannecker"), and the abstract of Kopp *et al.* (Cancer Research, 1995, Vol. 55, pp 4512-4515) ("Kopp"). In addition, Claims 1-6 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Bacus in view of the abstract of

Smith, and any of Porter, or Los, or Barbera-Guillem (all cited above) and further in view of the abstracts of Vollmer, Dannecker, Kopp (all cited above), and further view of Dash. (U.S. Patent 5,772,998). Applicant respectfully traverses these rejection.

A double patenting rejection under the judicially created doctrine of obviousness-type double patenting is "'analogous to [a failure to meet] the obviousness requirement of 35 U.S.C. 103' except that the patent principally underlying the double patenting rejection is not considered prior art." M.P.E.P. 804(II)(B)(1) *citing In re Braithwaite*, 379 F.2d 594 (C.C.P.A. 1967). Thus, the analysis employed in making an obviousness-type double patenting determination "parallels the guidelines for analysis of a 35 U.S.C. 103 obviousness determination." *Id. citing In re Braat*, 937 F.2d 589 (Fed. Cir. 1991); *In re Longi*, 759 F.2d 887 (Fed. Cir. 1985). Therefore, the same factual inquires set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148, are applied in a obviousness-type double patenting determination. *Id.*

None of the cited references in the three obviousness-type double patenting rejections, taken alone or in combination, teach or suggest the instantly claimed method. The deficiencies of Bacus Smith, Porter, Los, and Barbera-Guillem in supporting an obviousness rejection of claims 1, 2, 5, and 6 has been set forth above, and applies with equal force with regard to this separately-enunciated ground of rejection and will not be repeated here. Also, the deficiencies of Bacus, Smith, Porter, Los, Barbera-Guillem, and Vollmer, Dannecker, and Kopp in supporting an obviousness rejection of claims 1-3, 5, and 6 has been set forth above, and applies with equal force with regard to this separately-enunciated ground of rejection and will not be repeated here. Further, the deficiencies of Bacus, Smith, Porter, Los, Barbera-Guillem, Vollmer, Dannecker, Kopp, and Dash in supporting an obviousness rejection of claims 1-6 has been set forth above, and applies with equal force with regard to this separately-enunciated ground of rejection and

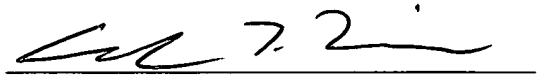
will not be repeated here. For the reasons set forth above, none of the references cited in support of these grounds of rejection, Bacus, Smith, Porter, Los, Barbera-Guillem, Vollmer, Dannecker, Kopp, and Dash, taken either alone or in any combination, disclose, either individually or in combination, the claimed method for determining a response to administration of a chemotherapeutic or chemopreventive agent to an individual. Accordingly, Applicant respectfully requests withdrawal of these three rejections and requests reconsideration of the claims.

Conclusion

In view of the above amendments and remarks, the application is considered to be in good and proper form for allowance and the Examiner is respectfully requested to pass this application to issue. If there are any questions or comments regarding this Response or application, the Examiner is encouraged to contact the undersigned attorney as indicated below.

Respectfully Submitted,

Date: April 5, 2005



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